Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5-7, and 14-25 are pending in the application, with 1, 7, 16 and 21 being the independent claims. Claims 1 and 7 have been amended to more particularly point out and claim the invention. New claims 14-25 have been added. Support for these new claims and the amended claims may be found in the specification, *inter alia*, for example, at page 5, lines 5-28 through page 6, lines 1-27. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Declaration

The Examiner has stated that the declaration is defective because non-initialed and/or non-dated alterations have been made to the declaration. The Examiner has stated that a new declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. (Paper No. 9, page 3.) Applicants respectfully traverse this objection. Solely in an effort to expedite prosecution, however, Applicants have submitted a newly executed declaration according to the Examiner's suggestion. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

Rejection under 35 U.S.C. § 102 (b)

The Examiner has rejected claims 1-13 under 35 U.S.C.§102(b) as allegedly being anticipated by Iwasaki, Y., *et al.*, *Jpn. J. Cancer Chemother.* 25:1412-1415 (1998) [hereinafter "Iwaski *et al.* (1998)"]; Carter, R., *et al.*, *Br. J. Cancer* 65:37-39 (1992) [hereinafter "Carter *et al.*"]; Ohigashi, H., *et al.*, *Hepato-Gastroenterology* 43:338-345 (1996) [hereinafter "Ohigashi *et al.*"]; Kitamura, M., *et al.*, *Jpn. J. Cancer Chemother.* 17:1657-1660 (1990) [hereinafter "Kitamura *et al.*"]; Tsuji, Y., *et al.*, *Jpn. J. Cancer Chemother.* 23:1617-1620 (1996) [hereinafter "Tsuji *et al.*"];Yamaue, H., *et al.*, *Arch. Jpn. Chir.* 59:302-309 (1990) [hereinafter "Yamaue *et al.*"]; Iwasaki, Y., *et al.*, *Jpn. J. Cancer Chemother.* 11:1674-1678 (1995) [hereinafter "Iwaski *et al.* (1995)"]; or Takahashi, N., *et al.*,*J. Of Japan Surgical Society* 92:775-784 (1991) [hereinafter "Takahashi *et al.*"]. Applicants respectfully traverse this rejection.

The claimed invention is directed, *intra alia*, to methods of treatment or prevention of cancer cell metastasis and methods of inducing the expression of β_1 integrin molecules in cancer cells. The methods of the present invention consist essentially of administering to a patient in need of treatment an effective amount of an angiotensin. The angiotensin is not delivered in a combination with another anti-tumor drug, however, an excipient or carrier may be added. Rather, an angiotensin is used on its own for the treatment or prevention of metastasis, presumably by inducing integrin production in cancer cells.

Iwaski *et al.* (1995) describe the treatment of a single patient presenting with liver metastasis of gastric cancer by intrahepatic infusion chemotherapy of mitomycin C (MMC) and 5-fluorouracil (5-FU) combined with angiotensin II (AT-II). Iwaski *et al.* (1995) did

not suggest the desirability of administering AT-II in the absence of anti-tumor drugs. Rather, the rationale of Iwaski *et al.* (1995) for the AT-II combination therapy was that AT-II enhances the amount of blood flow into the tumor and, therefore, increases the delivery of the anti-tumor drugs to the liver. Iwaski *et al.* (1995) discuss the use of AT-II in combination with anti-tumor drugs, stating "good results were obtained in terms of selectively increasing the blood flow in the tumor tissue and enhancing the incursion of the anti-tumor agent into the tumor." (English Translation of Iwaski *et al.* (1995), page 7, lines 13-15.) In a follow-up study, Iwaski *et al.* (1998) describe the intrahepatic infusion chemotherapy of MMC and 5-FU combined with AT-II of ten patients presenting with liver metastasis of gastric cancer. Once again, Iwaski *et al.* (1998) do not suggest treating liver metastasis with AT-II alone. Iwaski *et al.* (1998) conclude that combination therapy is necessary for the prevention of metastasis, stating

> Therefore, in the case of treatment and follow-up with this method, the development of other metastatic foci is to be carefully watched, *it is necessary to use special means such as concomitant use of systemic chemotherapy to inhibit metastasis* in other organs as soon as the liver metastasis is controlled, and as a result the prognosis is considered to be improved.

(English Translation of Iwaski *et al.* (1998), page 4, lines 12-16, emphasis added.)

Kitamura *et al.* evaluate the intra-arterial infusion of MMC and 5-FU with the concomitant use of AT-II of patients presenting with advanced or recurrent gastric cancer and inoperable liver or peritoneal metastasis. Kitamura *et al.* do not suggest using AT-II alone to treat advanced or recurrent gastric cancer or inoperable liver or peritoneal metastasis. Rather, AT-II is administered *only* in the presence of anti-tumor drugs.

Carter *et al.* describe the treatment of liver tumor-bearing rats with AT-II, degradable starch microspheres (DSM) and ^{99m}Tc methylene diphosphonate (MDP). Carter *et al.* administer AT-II only in the presence of anti-tumor drugs. The AT-II is used to enhance the amount of blood flow into the tumor and, therefore, to increase the delivery of the anti-tumor drugs to the liver. Carter *et al.* conclude that

> Moreover, the tumour:liver ratio of retained marker was significantly improved using combined angiotensin II and DSM with a concentration of marker in tumour over five times that in normal hepatic parenchyma. The maintenance of relatively high marker concentration in tumour over a 90 min period may reflect blood flow stasis and further prevention of washout, *due to targeting of the DSM toward the tumour by the Angiotensin II.*

(Carter *et al.*, page 39, column 2, lines 13-20, emphasis added.) Carter *et al.* do not suggest using AT-II alone to treat liver tumors. Rather, AT-II is administered *only* in the presence of MDP.

Takahashi *et al.* describe the treatment of gastric cancer with AT-II given in combination with anti-tumor drugs. Takahashi *et al.* do not administer AT-II alone nor do they suggest administering AT-II alone to treat gastric cancer. Rather, Takahashi *et al.* emphasize that the utility of administering AT-II in ***combination*** with anti-tumor drugs, stating

> Based on the results of this investigation, it is possible that the topical *AT-II mixture* arterial injection method can be applied to treat firstly an inoperable tumor confined to the controlling artery area, and secondarily an infiltrated serosa or associated lymph nodes in the vicinity of primary cancer remaining after surgery by *concomitant* treatment.

(English translation of Takahashi *et al.*, page 22, lines 30-33, emphasis added.)

Yamaue *et al.* describe the treatment of various cancers, including esophageal, gastric, hepatocellular, bile duct, pancreatic, colon, and breast carcinomas, with AT-II administered to patients as a drug delivery system just prior to the administration of MMC and adriamycin (ADR); FAM (5-FU, ADR and MMC); or cisplatin. Yamaue *et al.* do not administer AT-II in the absence of anti-tumor drugs, nor do they suggest using AT-II alone. Rather, Yamaue *et al.* use AT-II to enhance the amount of blood flow into the tumor and, therefore, to increase the delivery of the anti-tumor drugs to the target tissue. Yamaue *et al.* conclude that "the ***combination*** of AT II -induced hypertension with effective anticancer drugs may result in increased clinical efficacy" (p. 308, lines 21-22, emphasis added).

Ohigashi *et al.* describe the treatment of non-resectable (*i.e.* malignant) pancreatic cancer with angiotensin II given in combination with methotrexate (MTX) and 5-FU. Ohigashi *et al.* observed increased survival rates and a lower incidence of hepatic metastasis in patients receiving this combination therapy, as compared to that observed in previous studies of other chemo- or radio- therapies. Ohigashi *et al.* do not administer AT-II alone nor do they suggest administering AT-II alone to treat hepatic metastasis. Rather, Ohigashi explained

> We infused the anticancer agents mixed with angiotensin-II via the catheters, as it had been shown that angiotensin-II did not constrict the tumor vessels but constricted the vessels that supplied the blood flow in non-cancerous tissue (25,26). Our previous study (28) has shown that angiotensin-II infusion increased the blood flow in the pancreatic cancer tissue from 42 to 76 ml/min/100g, while decreasing the blood flow in non-cancerous tissue from 60 to 40 ml/min/100g. Mattson (29) and Yaegashi (30) have explained that this phenomenon is due to the tumor-supplying vessels lacking smooth muscle (3).

(Carter *et al.*, page 343, col. 1, lines 8-20.)

Tsuji *et al.* describe the treatment of a single patient presenting with operable advanced pancreatic carcinoma by intra-arterial infusion therapy of AT-II *combined* with MTX and the subsequent delivery of 5-FU. Tsuji *et al.* do not administer AT-II alone nor do they suggest administering AT-II alone to treat hepatic metastasis. Rather, Tsuji *et al.* concluded that liver metastasis were inhibited and the patient achieved long-term survival because "the selective anti-cancer drug administration with the *concomitant* use of AT-II." (Tsuji *et al.*, page 5, lines 7-8, emphasis added.) In summary, all of the cited documents are concerned only with the treatment of cancer using the ***combination*** of a chemotherapeutic drug and angiotensin.

The Examiner has asserted that the claims are anticipated by the references because all of the references teach angiotensin II in a carrier or excipient administered to a patient. (Paper No. 12, page 3.) Applicants respectfully disagree.

The cited documents neither disclose nor suggest the use of angiotensin *alone* to treat cancer. In the cited documents, the known effect of angiotensin on blood flow is utilized to control the blood flow to the tumor and the drug it is given in combination with is used to diminish the tumor size. In these documents, angiotensin is used in combination with other drugs as an adjuvant to chemotherapy. The cited documents do not show that angiotensin alone may be used in the treatment or prevention of metastasis, as disclosed in the present invention.

Solely in an attempt to expedite prosecution and without acquiescing in the propriety of the rejection, claims 1 and 7 have been amended to recite "a method...*consisting essentially of* administering to a patient in need of treatment an effective amount an angiotensin." (emphasis added.) This amendment renders moot the Examiner's rejection.

Therefore, the claims are not anticipated by Iwaski *et al.* (1995), Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*, Tsuji *et al.*, Yamaue *et al.* and Takahashi *et al.*. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103 (a)

The Examiner has rejected claims 1-13 under 35 U.S.C.§103(a) as allegedly being unpatentable over Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*,Tsuji *et al.*, Yamaue *et al.*, Iwaski *et al.* (1995), and Takahashi *et al.*. Applicants respectfully traverse the rejection.

The Examiner asserts that

> it would have been obvious to one of ordinary skill in the art to treat an individual with such cancer cells as these specific sources since the range of types of cancer cells listed in claim 2 is quite broad. It would have been well within the purview of the skilled artisan to treat such patients have such cancer cells [sic] since such cells are found in every patient. To use such pharmaceutical compositions also would have been obvious since such compositions are well within the skilled artisan [sic] to use in an effort to optimize the results of delivering the pharmaceutical to the patient.

(Paper No. 12, page 4.) Applicants respectfully traverse this rejection.

Among other requirements, in order to establish a *prima facie* case of obviousness, the Examiner must establish that there is some suggestion or motivation, either in the references themselves or in knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See, e.g.*, M.P.E.P. § 2143 at 2100-122 (Eighth Edition, August 2001). In addition, the mere fact that a reference could conceivably be modified to make the claimed invention does not render the resultant modification obvious unless the prior art also suggests the desirability of that specific

modification. *See In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, because there is no motivation to combine the cited references.

Contrary to the Examiner's argument, the cited references discuss, at best, the use of angiotensin *in combination* with anti-tumor drugs to treat cancer cells derived from breast, large bowel, stomach, and rectum. The cited documents do not show that angiotensin *alone* may be used in the treatment and prevention of metastasis of cancer cells in which the cancer cell is derived from breast, large bowel, stomach, rectum, skin, prostate, lung, bone and cervix, as disclosed in the present invention. Solely in an attempt to expedite prosecution and without acquiescing in the propriety of the rejection, claim 1 has been amended to recite "A method of treatment or prevention of metastasis of cancer cells *consisting essentially of*..."(emphasis added). This amendment renders moot the Examiner's rejection. Further, the Applicants have also provided a new set of claims using "comprising" language to include a method of treatment or prevention of metastasis of cancer cells derived from skin, prostate, lung, bone, or cervix. Nowhere has the Examiner cited art that suggests that angiotensin alone or with other chemotherapeutic agents may be used for the treatment or prevention of cancer derived from skin, prostate, lung, bone or cervix.

As amended, the claims are directed to methods "consisting essentially of administering to a patient in need of treatment an effective amount of an angiotensin." As stated above, Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*,Tsuji *et al.*, Yamaue *et al.*, Iwaski *et al.* (1995), and Takahashi *et al.* neither disclose nor suggest the use of angiotensin *alone* to treat cancer. In the cited documents, the known effect of angiotensin on blood flow is utilized to control the blood flow to the tumor and the drug it is given in

combination with is used to diminish the tumor size. In these documents, angiotensin is used in combination with other drugs as an adjuvant to chemotherapy. The cited documents do not show that angiotensin alone may be used in the treatment and prevention of metastasis, as disclosed in the present invention.

In view of the above, Applicants submit that the cited references do not suggest the desirability of combining the references to obtain the claimed invention, and thus fail to render the claimed invention obvious. Even if the cited art was combined, there is no suggestion to eliminate the chemotherapeutic agents and arrive at a treatment using only angiotensin. In addition, the cited references do not suggest that angiotensin acts to induce integrin production in cancer cells and thereby prevent metastases, as described in the present invention. Accordingly, the Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 4 and 8-12 have been cancelled.

Claims 14-25 have been added.

The claims are amended as follows:

1. (Once Amended) A method of treatment or prevention of metastasis of cancer cells [comprising] consisting essentially of administering to a patient in need of treatment an effective amount of an angiotensin.

2. (Once Amended) The [A] method as claimed in claim 1, [in which the cancer cell is derived from] wherein said cancer cells are derived from at least one of the group consisting of breast, skin, large bowel, prostate, lung, bone, cervix, stomach and [or] rectum.

3. (Once Amended) The [A] method as claimed in claim 1, wherein said [the] angiotensin is angiotensin-II.

5. (Twice Amended) [The pharmaceutical composition of claim 4 adopted for] The method as claimed in claim 1, wherein said administering is oral, rectal, nasal, topical, vaginal, or parenteral [administration].

6. (Twice Amended) [The pharmaceutical composition of claim 5

wherein the parenteral administration] The method as claimed in claim 1, wherein said adminstering is subcutaneous, intramuscular, intravenous, or intradermal.

7. (Once Amended) A method of inducing the expression of β_1 integrin molecules in cancer cells [comprising the step of] consisting essentially of administering to a patient an effective amount of an angiotensin.